# STIC Search Report
## Biotech-Chem Library

STIC Database Tracking Number: 134998

| | |
|---|---|
| **TO: Ben Sackey**<br>**Location: 5b31/5c18**<br>**Art Unit: 1626**<br>**Friday, October 15, 2004**<br><br>**Case Serial Number: 10/689513** | **From: Noble Jarrell**<br>**Location: Biotech-Chem Library**<br>**Rem 1B71**<br>**Phone: 272-2556**<br><br>**Noble.jarrell@uspto.gov** |

## Search Notes

# SEARCH REQUEST FORM

**Scientific and Technical Information Center**

Requester's Full Name: BEN SACKEY Examiner #: 73489 Date: 10/13/04
Art Unit: 1626 Phone Number 2-0704 Serial Number: 10/689,513
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

**If more than one search is submitted, please prioritize searches in order of need.**

**********

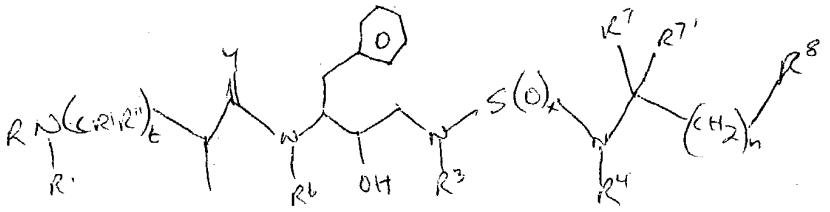
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Alpha-4 Beta-amino acid hydroxyethylamino Sulfonyl urea deriv

Inventors (please provide full names): _____

Earliest Priority Filing Date: 10/30/92

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the **appropriate serial number.***



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| STAFF USE ONLY | Type of Search | Vendors and cost where applicable |
|---|---|---|
| Searcher: Noble | NA Sequence (#) _____ | STN 263 |
| Searcher Phone #: _____ | AA Sequence (#) _____ | Dialog _____ |
| Searcher Location: _____ | Structure (#) 1 | Questel/Orbit _____ |
| Date Searcher Picked Up: _____ | Bibliographic _____ | Dr.Link _____ |
| Date Completed: 10/15/04 | Litigation _____ | Lexis/Nexis _____ |
| Searcher Prep & Review Time: 15 | Fulltext _____ | Sequence Systems _____ |
| Clerical Prep Time: _____ | Patent Family _____ | WWW/Internet _____ |
| Online Time: 20 | Other _____ | Other (specify) _____ |

PTO-1590 (8-01)

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 14 OCT 2004 HIGHEST RN 762927-58-2
DICTIONARY FILE UPDATES: 14 OCT 2004 HIGHEST RN 762927-58-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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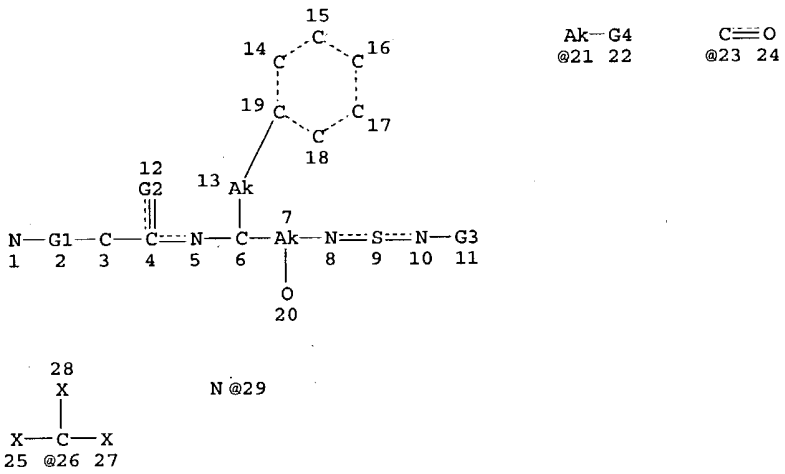
L5 STR




Ak—G4
@21 22

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@23 24

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VAR G3=AK/21
VAR G4=CN/O/CY/23/S/26/29
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NSPEC IS RC AT 1
NSPEC IS RC AT 29
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14
NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.01

20 ANSWERS

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L10           50 E3,E5-7
                 E MUELLER R/AU
L11          858 E3-4
                 E MUELLER RICHARD/AU
L12          340 E3-7
                 E TALLEY J/AU
L13          136 E3,E7,E24-25
                 E GETMAN D/AU
L14          108 E3,E5,E10-12
                 E DECRESCENZO G/AU
L15           69 E3-6
                 E SUN E/AU
L16           17 E3,E8-9
                 E SUN ERIC/AU
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L22            1 L21 NOT L20
L23            4 L8 NOT L20
L24            3 L23 AND (PY<=1992 OR PRY<=1992 OR AY<=1992 OR PD<19921030 OR AD

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 15 Oct 2004 VOL 141 ISS 17
FILE LAST UPDATED: 14 Oct 2004 (20041014/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d all hitstr 120 tot

L20 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:725344 HCAPLUS
DN 126:75247
ED Entered STN: 11 Dec 1996
TI Preparation of .alpha.- and .beta.-amino acid hydroxyethylamino sulfonyl urea derivatives as retroviral protease inhibitors
IN **Vazquez, Michael L.; Mueller, Richard A.; Talley, John J.; Getman, Daniel P.; Decrescenzo, Gary A.; Sun, Eric T.**
PA G.D. Searle and Co., USA
SO U.S., 37 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D401-12
ICS C07D413-12; C07D417-12; A61K031-47; A61K031-505; A61K031-54
NCL 514314000
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 5578606 | A | 19961126 | US 1992-968712 | 19921030 |
| | US 6022872 | A | 20000208 | US 1996-709069 | 19960906 |
| | US 6211176 | B1 | 20010403 | US 1999-345739 | 19990701 |
| | US 6403585 | B1 | 20020611 | US 2000-731911 | 20001208 |
| | US 2003144342 | A1 | 20030731 | US 2002-138534 | 20020506 |
| | US 6683648 | B2 | 20040127 | | |
| | US 2004171653 | A1 | 20040902 | US 2003-689513 | 20031021 |
| PRAI | US 1992-968712 | A3 | 19921030 | | |
| | US 1996-709069 | A1 | 19960906 | | |
| | US 1999-345739 | A1 | 19990701 | | |
| | US 2000-731911 | A1 | 20001208 | | |
| | US 2002-138534 | A1 | 20020506 | | |

CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES |
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| US 5578606 | ICM | C07D401-12 |
| | ICS | C07D413-12; C07D417-12; A61K031-47; A61K031-505; A61K031-54 |
| | NCL | 514314000 |
| US 5578606 | ECLA | C07C307/06; C07D239/38; C07D307/85; C07K005/06A1A1; C07K005/06A1A3; C07K005/06H2; C07K005/06T; C07D023/42C; C07D215/48; C07D215/50; C07D215/54; C07D235/06B |
| US 6403585 | ECLA | C07C307/06; C07D213/42C; C07D215/48; C07D215/50; C07D215/54; C07D235/06B; C07D239/38; C07D030/85; C07K005/06A1A3; C07K005/06A1A1; C07K005/06H2; C07K005/06T |
| US 2003144342 | ECLA | C07C307/06; C07D213/42C; C07D215/48; C07D215/50; C07D215/54; C07D235/06B; C07D239/38; C07D030/85; C07K005/06A1A3; C07K005/06A1A1; C07K005/06H2; C07K005/06T |

OS MARPAT 126:75247
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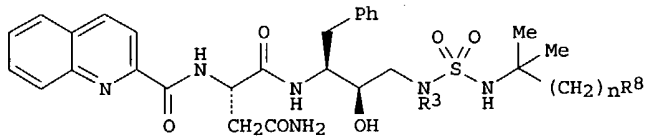

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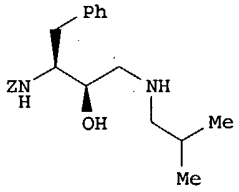

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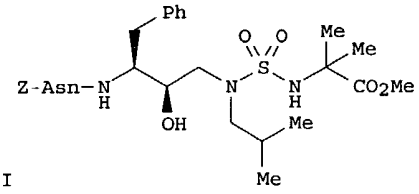


III

Searched by Noble Jarrell

AB .alpha.- And .beta.-amino acid hydroxyethylamino sulfonyl urea derivative compds., e.g. I [R3 = C1-8 alkyl, (un)substituted C1-8 alkylphenyl, C1-8 heteroaralkyl; R8 = (un)substituted Ph, heterocyclyl, CN, OH, CO2H, C1-8 alkylthio, (un)substituted phenylsulfonyl, C1-8 alkanoyl, C1-8 alkoxycarbonyl, C1-8 dialkylaminocarbonyl, N-C1-8- alkyl-N-phenylcarbamoyl, 2-heterocyclylethoxy, heterocyclyl; n = 0-2], are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease. Thus, coupling of protected amino(hydroxy)phenylbutylamine II (Z = PhCH2O2C) (prepared in 3 steps from chloromethyl ketone Z-L-Phe-CH2Cl) with ClSO2NHCMe2CO2Me, followed by hydrogenolysis and coupling with Z-Asn-OH gave inhibitor III.

ST retroviral protease inhibitor hydroxyethylaminosulfonyl urea peptide; protease inhibitor hydroxyethylaminosulfonyl urea peptide prepn; HIV virucide hydroxyethylaminosulfonyl urea peptide prepn

IT Antiviral agents
Human immunodeficiency virus 1
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT **185256-67-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT 63-91-2, L-Phenylalanine, reactions 78-81-9, Isobutylamine 105-13-5, 4-Methoxybenzyl alcohol 107-85-7, Isoamylamine 2170-03-8 2304-96-3 26049-94-5 152714-71-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT 107-95-9P, .beta.-Alanine 498-25-9P 541-48-0P, 3-Aminobutanoic acid 3377-31-9P 3653-34-7P 4385-92-6P 5699-54-7P 15099-85-1P 16934-21-7P 32723-74-3P 32723-76-5P 53874-24-1P 60427-77-2P 65414-77-9P 75081-40-2P 83509-04-0P 91247-38-0P 95598-13-3P 100869-07-6P 111060-52-7P 111060-64-1P 127927-43-9P 128018-43-9P 128018-44-0P 130165-86-5P 132605-93-7P 132605-97-1P 132605-98-2P 132696-45-8P 143224-62-8P 143224-86-6P 143225-04-1P 160191-57-1P 185256-61-5P 185256-62-6P 185256-63-7P 185256-64-8P 185256-65-9P 185256-66-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

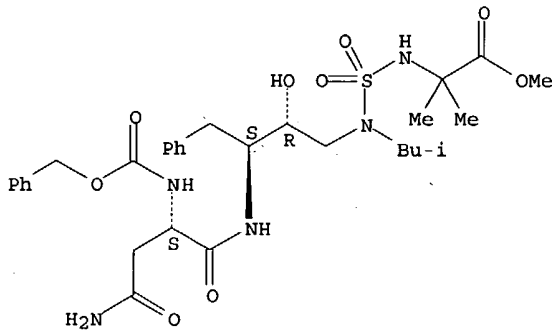
IT 9001-92-7, Protease
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(retroviral; preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT **185256-67-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

RN 185256-67-1 HCAPLUS

CN 10-Thia-2,5,9,11-tetraazatridecanedioic acid, 3-(2-amino-2-oxoethyl)-7-hydroxy-12,12-dimethyl-9-(2-methylpropyl)-4-oxo-6-(phenylmethyl)-, 13-methyl 1-(phenylmethyl) ester, 10,10-dioxide, [3S-(3R*,6R*,7S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L20 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:330514 HCAPLUS
DN 122:106521
ED Entered STN: 04 Feb 1995
TI Preparation of N-sulfamidohydroxyalkyl amino acid amides as retroviral protease inhibitors
IN **Vazquez, Michael L.; Mueller, Richard A.; Talley, John J.; Getman, Daniel P.; Decrescenzo, Gary A.; Sun, Eric T.**
PA G.D. Searle and Co., USA; Monsanto Co.
SO PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C307-06
ICS C07D295-22; C07K005-06; C07D215-48; A61K031-18; A61K031-495; A61K031-45; A61K031-40; A61K037-02
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9410134 | A1 | 19940511 | WO 1993-US10552 | 19931029 |
| | W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2142997 | AA | 19940511 | CA 1993-2142997 | 19931029 |
| | AU 9455470 | A1 | 19940524 | AU 1994-55470 | 19931029 |
| | EP 666842 | A1 | 19950816 | EP 1994-900506 | 19931029 |
| | EP 666842 | B1 | 19980624 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | EP 810208 | A2 | 19971203 | EP 1997-113206 | 19931029 |
| | EP 810208 | A3 | 19981202 | | |
| | EP 810208 | B1 | 20020102 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE | | | | |
| | AT 167669 | E | 19980715 | AT 1994-900506 | 19931029 |
| | ES 2118364 | T3 | 19980916 | ES 1994-900506 | 19931029 |
| | AT 211462 | E | 20020115 | AT 1997-113206 | 19931029 |
| | PT 810208 | T | 20020628 | PT 1997-113206 | 19931029 |
| | ES 2170305 | T3 | 20020801 | ES 1997-113206 | 19931029 |
| | US 6156768 | A | 20001205 | US 1995-379545 | 19950202 |
| | US 6444678 | B1 | 20020903 | US 2000-633063 | 20000804 |
| | US 2003158236 | A1 | 20030821 | US 2002-178956 | 20020625 |
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| | EP 1994-900506 | A3 | 19931029 | | |
| | WO 1993-US10552 | W | 19931029 | | |
| | US 1995-379545 | A3 | 19950202 | | |
| | US 2000-633063 | A1 | 20000804 | | |

CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES |
|---|---|---|
| WO 9410134 | ICM | C07C307-06 |
| | ICS | C07D295-22; C07K005-06; C07D215-48; A61K031-18; A61K031-495; A61K031-45; A61K031-40; A61K037-02 |
| US 6444678 | ECLA | C07C307/06; C07D215/48; C07D295/22C2; C07K005/06A1A1; |

C07K005/06H2
US 2003158236 ECLA C07C307/06; C07D215/48; C07D295/22C2; C07K005/06A1A1; C07K005/06H2
OS MARPAT 122:106521
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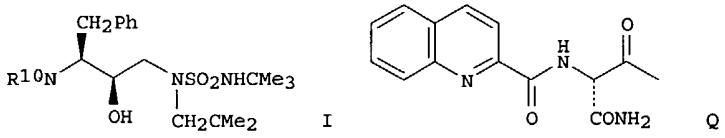



AB RR'N(CR7R8)tCHR1C(:Y)NR6CHR2CH(OH)CH2NR3SOxNR4R5 [R = H, (cyclo)alkyl, (hetero)aryl, alkyl(oxy)carbonyl, heterocyclyl(oxy)carbonyl, etc.; R' = groups cited for R3, R''SO2; R'' = groups cited for R3; NRR' = heterocyclyl, heteroaryl; R1,R7,R8 = H, (halo)alkyl, amino acid side chain, CONH2, CO2Me, etc.; R1R7 = atoms to form a cycloalkyl group; R2 = (un)substituted (cyclo)alkyl, aryl(alkyl); R3 = (cyclo)alkyl, (hetero)aryl(alkyl), aminoalkyl, etc.; R4,R5 = H, groups cited for R3; NR4R5 = heterocyclyl, heteroaryl; R6 = H, alkyl; Y = O, S, NH, NR3; t = 0-2; x = 1 or 2] were prepared Thus, N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane (preparation given) was condensed with Me2CHCH2NH2 and the product amidated by ClSO2NHCMe3 (preparation given) to give, after deprotection, sulfamamide I (R10 = H) which was N-acylated by N-BOC-L-asparagine and the deprotected product N-acylated by quinoline-2-carboxylic acid to give I (R10 = quinolinoylasparaginyl group Q). The latter had IC50 of 2nM against HIV-1 infection of CEM cells in vitro.

ST amino acid amide sulfamidohydroxyalkyl antiviral; retroviral protease inhibitor amino acid

IT Acquired immune deficiency syndrome
(treatment of, N-sulfamidohydroxyalkyl amino acid amides for)

IT Virus, animal
(human immunodeficiency 1, infection by, treatment of, N-sulfamidohydroxyalkyl amino acid amides for)

IT Virus, animal
(retro-, protease of, inhibition of, N-sulfamidohydroxyalkyl amino acid amides for)

IT 7338-27-4P 10305-43-8P, Butylsulfamoyl chloride 33581-95-2P, tert-Butylsulfamoyl chloride 33581-96-3P 39085-61-5P, Butylsulfamic acid 60427-77-2P, 4-(4-Methoxybenzyl) itaconate 83509-04-0P 95437-43-7P 111060-52-7P 111060-64-1P 127927-43-9P 128018-43-9P 128018-44-0P 130165-86-5P 132605-93-7P 132605-97-1P 132605-98-2P 132696-45-8P 143224-48-0P 143224-62-8P 143224-86-6P 143225-04-1P 143244-71-7P 143576-90-3P 160676-95-9P 160676-96-0P 160676-97-1P 160676-98-2P 160676-99-3P 160677-00-9P 160677-01-0P 160677-02-1P 160677-03-2P 160677-04-3P 160677-05-4P 160677-06-5P **160677-07-6P** **160677-08-7P** 160677-09-8P 160677-10-1P **160677-11-2P** 160677-12-3P **160677-13-4P** **160677-14-5P** **160677-15-6P** 160677-20-3P 160677-21-4P 160677-22-5P 160677-23-6P 160677-24-7P 160677-25-8P 160677-26-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of retroviral protease inhibitor)

IT **160676-88-0P** **160676-89-1P** 160676-90-4P **160676-91-5P** **160676-92-6P** 160676-93-7P 160676-94-8P **160677-16-7P** **160677-17-8P** **160677-18-9P** **160677-27-0P** **160677-28-1P** 160677-29-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as retroviral protease inhibitor)

IT 63-91-2, L-Phenylalanine, reactions 75-65-0, tert-Butanol, reactions 78-81-9, Isobutylamine 100-39-0, Benzyl bromide 105-13-5, 4-Methoxybenzyl alcohol 107-85-7, Isoamylamine 111-36-4, Butylisocyanate 2170-03-8, Itaconic anhydride 7536-55-2 26049-94-5, N-Benzyloxycarbonyl-L-phenylalanine chloromethyl ketone 35856-62-3, 1-ChlorosulfonylPiperidine 50398-09-9, 1-Methylpiperazine hydrochloride 62965-10-0 136465-99-1, 2-Quinolinecarboxylic acid N-hydroxysuccinimide ester 160677-19-0

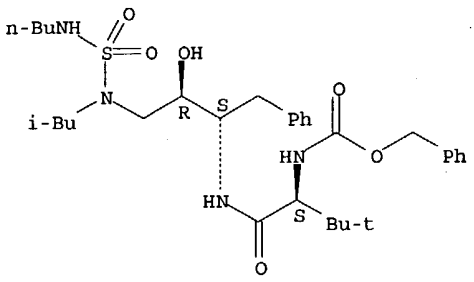
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of retroviral protease inhibitor)

IT **160677-07-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of retroviral protease inhibitor)

RN 160677-07-6 HCAPLUS

CN 10-Thia-2,5,9,11-tetraazapentadecanoic acid, 3-(1,1-dimethylethyl)-7-hydroxy-9-(2-methylpropyl)-4-oxo-6-(phenylmethyl)-, phenylmethyl ester, 10,10-dioxide, [3S-(3R*,6R*,7S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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L22 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1996:153437 HCAPLUS

DN 124:220480

ED Entered STN: 16 Mar 1996

TI Retroviral protease inhibitor combinations

IN Bryant, Martin L.; Potts, Karen E.; Smidt, Mary; Tucker, Simon P.

PA G.D. Searle and Co., USA

SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-425
ICS A61K031-495; A61K031-16; A61K031-44; A61K031-18; A61K031-395

CC 1-5 (Pharmacology)
Section cross-reference(s): 28, 34

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9533464 | A2 | 19951214 | WO 1995-US6673 | 19950602 |
| | WO 9533464 | A3 | 19960104 | | |
| | W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT | | | | |
| | RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2191948 | AA | 19951214 | CA 1995-2191948 | 19950602 |
| | AU 9526510 | A1 | 19960104 | AU 1995-26510 | 19950602 |
| | AU 696299 | B2 | 19980903 | | |
| | EP 762880 | A1 | 19970319 | EP 1995-921428 | 19950602 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| | BR 9507912 | A | 19970812 | BR 1995-7912 | 19950602 |
| | CN 1166786 | A | 19971203 | CN 1995-194464 | 19950602 |
| | HU 76979 | A2 | 19980128 | HU 1996-3328 | 19950602 |
| | JP 10505324 | T2 | 19980526 | JP 1995-501057 | 19950602 |
| | NZ 287702 | A | 20000623 | NZ 1995-287702 | 19950602 |
| | US 6100277 | A | 20000808 | US 1995-458154 | 19950602 |
| | PL 180070 | B1 | 20001229 | PL 1995-317425 | 19950602 |
| | RU 2166317 | C2 | 20010510 | RU 1997-100123 | 19950602 |
| | NO 9605136 | A | 19970120 | NO 1996-5136 | 19961202 |
| | FI 9604835 | A | 19970129 | FI 1996-4835 | 19961203 |
| | US 2003207813 | A1 | 20031106 | US 2002-253899 | 20020925 |
| PRAI | US 1994-253638 | A2 | 19940603 | | |
| | WO 1995-US6673 | W | 19950602 | | |

US 1996-737960 B1 19961209

CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES |
|---|---|---|
| WO 9533464 | ICM | A61K031-425 |
| | ICS | A61K031-495; A61K031-16; A61K031-44; A61K031-18; A61K031-395 |

AB A method is disclosed for the treatment of mammalian retrovirus infections, e.g. HIV, using combinations of retroviral protease inhibitors which are effective in preventing the replication of the retroviruses in vitro or in vivo. In particular, the invention provides protease inhibitor compds. used in combination therapy with other protease inhibitor compds. Also disclosed is combination therapy with a combination of protease inhibitors and antiviral agents other than protease inhibitors. Preparation and activity of selected inhibitors is included.

ST retrovirus protease inhibitor combination; virucide retrovirus protease inhibitor prepn

IT Drug resistance
Felis catus
Monkey
Virucides and Virustats
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT Nucleosides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analogs, retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT Ribonucleic acid formation factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene tat, antagonists; retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT Virus, animal
(human T-cell leukemia, retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT Virus, animal
(human immunodeficiency, retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT Virus, animal
(human immunodeficiency 1, retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT Virus, animal
(human immunodeficiency 2, retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT Virus, animal
(retro-, retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; protease inhibitor combinations against HIV, and protease inhibitor preparation)

IT 9032-92-2, Glycosidase 9068-38-6, Reverse transcriptase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT 143224-34-4 143224-35-5 159005-88-6 **160676-92-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT 174303-65-2P 174303-66-3P 174303-67-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT 127779-20-8 155213-67-5, A 84538 157566-81-9 157810-81-6, L 735524 159910-86-8 159989-65-8, AG 1343 174391-92-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT 63-91-2, L-Phenylalanine, reactions 78-81-9, Isobutylamine 100-39-0, Benzyl bromide 123-75-1, Pyrrolidine, reactions 144-62-7, Oxalic acid, reactions 274-09-9, 1,3-Benzodioxole 541-88-8, Chloroacetic anhydride

3182-95-4, L-Phenylalaninol 75172-11-1 169331-42-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT 111060-52-7P 111060-64-1P 111138-83-1P 115010-10-1P, 1,3-Benzodioxole-5-sulfonyl chloride 127927-43-9P 143291-14-9P 174303-68-5P 174303-69-6P 174303-70-9P 174303-71-0P 174391-93-6P 174799-02-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

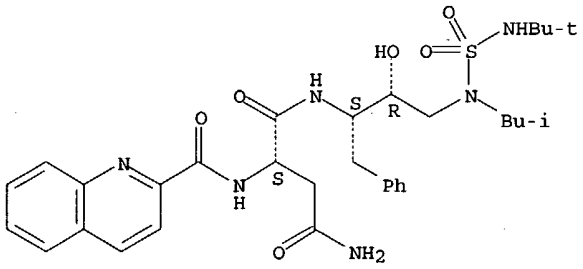
IT 7481-89-2, DDC 30516-87-1, AZT 69655-05-6, DDI 72599-27-0, N-Butyl-1-deoxynojirimycin 79831-76-8, Castanospermine 134878-17-4, A 77003 161814-49-9, VX 478
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(retroviral, inhibitors; retroviral protease inhibitor combinations, and protease inhibitor preparation)

IT **160676-92-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(retroviral protease inhibitor combinations, and protease inhibitor preparation)

RN 160676-92-6 HCAPLUS
CN Butanediamide, N1-[3-[[[(1,1-dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*),2S*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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L24 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:502547 HCAPLUS
DN 129:136097
ED Entered STN: 13 Aug 1998
TI Preparation of heterocyclic sulfonamide inhibitors of aspartyl protease
IN Tung, Roger D.; Murcko, Mark A.; Bhisetti, Govinda Rao
PA Vertex Pharmaceuticals, Incorporated, USA
SO U.S., 87 pp., Cont.-in-part of U.S. 5,585,397.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D215-12
NCL 546169000
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 28
FAN.CNT 5

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 5783701 | A | 19980721 | US 1995-393460 | 19950223 <-- |
| | EP 885887 | A2 | 19981223 | EP 1998-113921 | 19930907 <-- |
| | EP 885887 | A3 | 19990203 | | |
| | EP 885887 | B1 | 20030528 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | | |
| | US 5585397 | A | 19961217 | US 1993-142327 | 19931124 <-- |

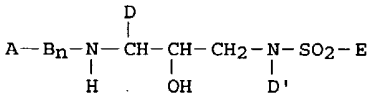
| | | | | |
|---|---|---|---|---|
| US 5723490 | A | 19980303 | US 1995-424819 | 19950419 <-- |
| US 5977137 | A | 19991102 | US 1998-115394 | 19980714 <-- |
| US 6392046 | B1 | 20020521 | US 1999-409808 | 19990930 <-- |
| US 2003064977 | A1 | 20030403 | US 2002-94763 | 20020308 <-- |
| US 6720335 | B2 | 20040413 | | |
| US 2004167116 | A1 | 20040826 | US 2004-786997 | 20040224 <-- |
| DRAT US 1992 941982 | B2 | 19920908 <-- | | |
| US 1993-142327 | A2 | 19931124 | | |
| EP 1993-921428 | A3 | 19930907 | | |
| WO 1993-US8458 | W | 19930907 | | |
| US 1995-393460 | B2 | 19950223 | | |
| US 1998-115394 | A3 | 19980714 | | |
| US 1999-409808 | A3 | 19990930 | | |
| US 2002-94763 | A1 | 20020308 | | |

CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES |
|---|---|---|
| US 5783701 | ICM | C07D215-12 |
| | NCL | 546169000 |
| US 5783701 | ECLA | C07D207/26C; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2; C07D209/08; C07D213/30D; C07D215/48; C07D231/14; C07D263/24; C07D271/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/12; C07D409/12; C07D409/12; C07D409/12; C07D413/12; C07D413/12 <-- |
| US 5585397 | ECLA | C07D207/26C; C07D209/08; C07D213/30D; C07D215/48; C07D231/14; C07D239/22D2; C07D263/24; C07D271/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/12; C07D409/12; C07D409/12; C07D409/12; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2 <-- |
| US 5977137 | ECLA | C07K005/06H2 <-- |
| US 6392046 | ECLA | C07D207/26C; C07D213/30D; C07D215/48; C07D209/08; C07D231/14; C07D239/22D2; C07D263/24; C07D071/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/2; C07D405/12; C07D409/12; C07D409/12; C07D409/12; C07D409/14; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2 <-- |
| US 2003064977 | ECLA | C07D207/26C; C07D209/08; C07D213/30D; C07D215/48; C07D231/14; C07D239/22D2; C07D263/24; C07D071/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/2; C07D405/12; C07D409/12; C07D409/12; C07D409/14; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2 <-- |

OS MARPAT 129:136097

GI



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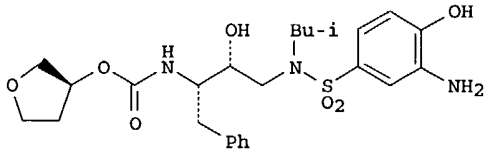

II

AB The title compds. I [A = H, -Ht, -R1Ht, (un)substituted -R1-alk(en)yl; R1 = CO, SO2, COCO, OCO, OSO2, NR2SO2, NR2CO, NR2COCO; Ht = (un)substituted cycloalk(en)yl, aryl, (benzo)heterocyclyl; R2 = H, alkyl, -alkyl-R7; B = NR2C(R3)2CO; n = 0, 1; R3 = (un)substituted alk(en)yl or cycloalk(en)yl; n = 1, 2; D, D' = R7, (un)substituted alk(en)yl or cycloalk(en)yl; R7 = (un)substituted Ph, carbocyclyl, or heterocyclyl; E = Ht, -O-Ht, -Ht-Ht, OR3, NR2R3, (un)substituted alk(en)yl or carbocyclyl; R4 = OR2, CONHR2,

SO2NHR2, halo, NR2COR2, cyano] are prepared as inhibitors of HIV aspartyl protease. The invention also relates to pharmaceutical compns. comprising these compds. The compds. and pharmaceutical compns. are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity. The invention also relates to methods for inhibiting the activity of HIV aspartyl protease using the invention compds., and to methods for screening compds. for anti-HIV activity. Prepns. of almost 200 compds. are described, and some of these plus addnl. compds. are claimed. Some of the compds., e.g., II, inhibit HIV replication (IC90) in CCRM-CEM cells in vitro at concns. of .ltoreq. 100 nM.

ST sulfonamide prepn aspartyl protease inhibitor; HIV antiviral sulfonamide prepn

IT Antiviral agents
Human T-lymphotropic virus
Human immunodeficiency virus 1
Human immunodeficiency virus 2
(preparation of heterocyclic sulfonamide derivs. as inhibitors of HIV aspartyl protease)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of heterocyclic sulfonamide derivs. as inhibitors of HIV aspartyl protease)

IT 1080-11-1P 1828-66-6P, 4-Morpholinesulfonyl chloride 4295-99-2P
6053-81-2P, Aminomethylcyclopentane 23905-46-6P 25506-37-0P
30293-86-8P 32939-32-5P 35856-62-3P, 1-Piperidinesulfonyl chloride
52206-05-0P 52665-49-3P, 3-Furansulfonyl chloride 54981-39-4P
87001-32-9P, 4-Benzyloxybenzenesulfonyl chloride 102522-17-8P
114322-14-4P, 2,1,3-Benzoxadiazole-4-sulfonyl chloride 115010-10-1P,
1,3-Benzodioxole-5-sulfonyl chloride 115010-11-2P, 2,3-Dihydrobenzofuran-5-sulfonyl chloride 116586-32-4P 130290-79-8P 132682-22-5P
132682-23-6P 134807-06-0P 134807-20-8P 138499-08-8P 143224-83-3P
158851-95-7P 159006-03-8P 159006-20-9P 159141-66-9P 160231-97-0P
160231-98-1P 160231-99-2P 160232-00-8P 160232-01-9P 160232-02-0P
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160232-10-0P 160232-11-1P 160232-12-2P 160232-13-3P 160232-14-4P
160232-15-5P, 2,1,3-Benzoxadiazole-4-sulfonic acid 160232-17-7P
160232-18-8P 160232-19-9P, 2,1,3-Benzoxadiazole-5-thiol 160232-20-2P,
2,1,3-Benzoxadiazole-5-sulfonyl chloride 160232-22-4P 160232-23-5P
160232-24-6P 160232-25-7P 160232-26-8P 160232-27-9P 160232-28-0P
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186463-35-4P 186463-37-6P 186463-39-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of heterocyclic sulfonamide derivs. as inhibitors of HIV aspartyl protease)

IT 157567-04-9P 157567-10-7P 159005-79-5P 159005-82-0P 159005-86-4P
160230-05-7P 160230-06-8P 160230-07-9P 160230-08-0P 160230-09-1P
160230-10-4P 160230-11-5P 160230-12-6P 160230-13-7P 160230-14-8P
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210537-89-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclic sulfonamide derivs. as inhibitors of HIV aspartyl protease)

IT 78169-47-8, Aspartyl protease
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of heterocyclic sulfonamide derivs. as inhibitors of HIV aspartyl protease)

IT 60-12-8, Phenethyl alcohol 74-89-5, Methylamine, reactions 75-44-5, Carbonic dichloride 78-81-9, Isobutylamine 79-22-1, Methyl chloroformate 93-10-7, Quinaldic acid 98-09-9, Benzenesulfonyl chloride 98-31-7, 3,4-Dichlorobenzenesulfonyl chloride 98-59-9, p-Toluenesulfonyl chloride 98-68-0, 4-Methoxybenzenesulfonyl chloride 98-74-8, p-Nitrobenzenesulfonyl chloride 98-79-3, L-Pyroglutamic acid 99-16-1 100-46-9, Benzylamine, reactions 100-55-0, 3-Pyridylcarbinol 105-13-5, 4-Methoxybenzyl alcohol 108-23-6, Isopropyl chloroformate 109-61-5, Propyl chloroformate 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 121-47-1, 3-Aminobenzenesulfonic acid 121-60-8, 4-Acetamidobenzenesulfonyl chloride 124-63-0, Methanesulfonyl chloride 274-09-9, 1,3-Benzodioxole 349-71-3, 3-Fluoro-4-acetamidobenzenesulfonyl chloride 453-20-3 496-16-2, 2,3-Dihydrobenzofuran 501-53-1, Benzyl chloroformate 541-41-3, Ethyl chloroformate 543-27-1, Isobutyl chloroformate 585-47-7, 1,3-Benzenedisulfonyl dichloride 586-98-1, 2-Pyridylcarbinol 612-16-8, 2-Methoxybenzyl alcohol 617-89-0, Furfurylamine 628-12-6, 2-Methoxyethyl chloroformate 638-32-4, Succinamic acid 701-99-5, Phenoxyacetyl chloride 768-09-2, 2,1,3-Benzoxadiazol-5-ol 777-44-6, 3-Trifluoromethylbenzenesulfonyl chloride 1003-03-8, Cyclopentylamine 1445-91-6, (s)-(-)-1-Phenylethanol 1483-28-9, 2,5-Dimethoxybenzenesulfonyl chloride 1517-69-7, (+)-1-Phenylethanol 1656-44-6, 2,4-Dinitrobenzenesulfonyl chloride 1885-14-9, Phenyl chloroformate 1939-99-7, .alpha.-Toluenesulfonyl chloride 2905-21-7, 2-Fluorobenzenesulfonyl chloride 2937-50-0, Allyl chloroformate 2942-58-7, Diethyl cyanophosphonate 3160-59-6 3173-56-6, Benzyl isocyanate 3218-02-8, Cyclohexanemethanamine 3445-11-2 3513-81-3, 2-Methylene-1,3-propanediol 4025-64-3 4254-02-8, Cyclopentanecarbonitrile 4319-49-7, N-Aminomorpholine 5070-13-3 5680-80-8, Serine methyl ester hydrochloride 5988-19-2, L-Dihydroorotic acid 6306-52-1, Valine methyl ester hydrochloride 6971-51-3, 3-Methoxybenzyl alcohol 7693-46-1, p-Nitrophenyl chloroformate 13360-57-1, Dimethylsulfamoyl chloride 13918-92-8, 2,4-Difluorobenzenesulfonyl chloride 15833-61-1, Tetrahydro-3-furanmethanol

16078-30-1, 1-Acetylindoline 16375-88-5, 4-Acetamidobenzyl alcohol
16420-13-6, Dimethylthiocarbamoyl chloride 16761-18-5,
4-Acetamido-3-chlorobenzenesulfonyl chloride 22037-28-1, 3-Bromofuran
23095-31-0, 3,4-Dimethoxybenzenesulfonyl chloride 24424-99-5,
Di-tert-butyl pyrocarbonate 28148-54-1, 2-Methylallylamine hydrochloride
30992-29-1 30996-79-3 49584-26-1, 4-Cyanobenzenesulfonyl chloride
52467-54-6 69812-29-9, 2-Acetamido-4-methyl-5-thiazolesulfonyl chloride
80466-79-1, 3,5-Dimethylisoxazole-4-sulfonyl chloride 80466-80-4,
2,4-Dimethylthiazole-5-sulfonyl chloride 86087-23-2 86087-24-3
88986-45-2, 3-Butenyl chloroformate 94108-56-2, 4-
Trifluoromethoxybenzenesulfonyl chloride 98737-29-2 126714-85-0
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RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of heterocyclic sulfonamide derivs. as
inhibitors of HIV aspartyl protease)

RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT **160230-15-9P 160230-25-1P 160230-31-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclic sulfonamide derivs. as inhibitors of HIV aspartyl protease)

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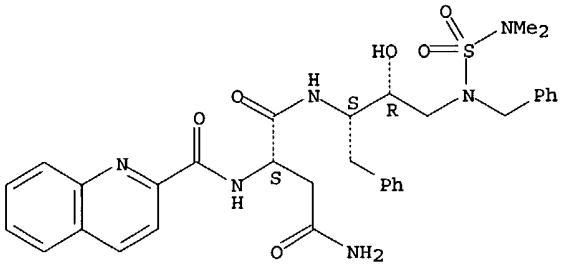
CN Butanediamide, N1-[(1S,2R)-3-[[(dimethylamino)sulfonyl](phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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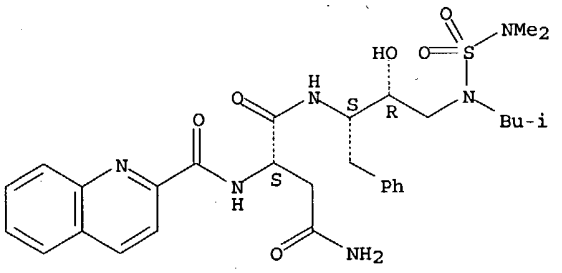
CN Butanediamide, N1-[(1S,2R)-3-[[(dimethylamino)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

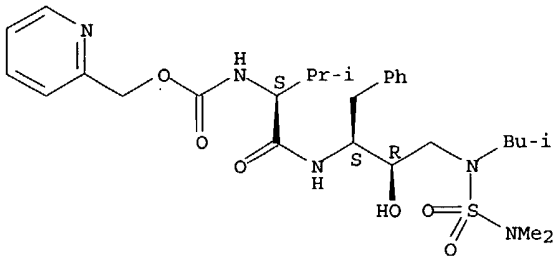


RN 160230-31-9 HCAPLUS
CN 3-Thia-2,4,8,11-tetraazadodecan-12-oic acid, 6-hydroxy-2-methyl-10-(1-methylethyl)-4-(2-methylpropyl)-9-oxo-7-(phenylmethyl)-, 2-pyridinylmethyl ester, 3,3-dioxide, (6R,7S,10S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 160230-30-8
CMF C28 H43 N5 O6 S

Absolute stereochemistry.



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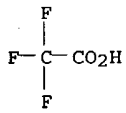

L24 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:9928 HCAPLUS
DN 126:144117
ED Entered STN: 09 Jan 1997
TI Preparation of sulfonamide inhibitors of aspartyl protease
IN Tung, Roger D.; Murcko, Mark A.; Bhisetti, Govinda R.
PA Vertex Pharmaceuticals, Incorporated, USA
SO U.S., 87 pp., Cont.-in-part of U.S. Ser. No. 941,982,abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D407-12
ICS C07D307-20; A61K031-34
NCL 514473000
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 28
FAN.CNT 5

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI US 5585397 | A | 19961217 | US 1993-142327 | 19931124 <-- |
| WO 9405639 | A1 | 19940317 | WO 1993-US8458 | 19930907 <-- |
| W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| EP 885887 | A2 | 19981223 | EP 1998-113921 | 19930907 <-- |
| EP 885887 | A3 | 19990203 | | |
| EP 885887 | B1 | 20030528 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | | |
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US 2002-94763 A1 20020308

CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES | |
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| US 5585397 | ICM | C07D407-12 | |
| | ICS | C07D307-20; A61K031-34 | |
| | NCL | 514473000 | |
| US 5585397 | ECLA | C07D207/26C; C07D209/08; C07D213/30D; C07D215/48; C07D231/14; C07D239/22D2; C07D263/24; C07D271/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/12; C07D405/12; C07D409/12; C07D409/12; C07D409/14; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2 | <-- |
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| US 5856353 | ECLA | C07D207/26C; C07D209/08; C07D213/30D; C07D215/48; C07D231/14; C07D239/22D2; C07D263/24; C07D071/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/2; C07D405/12; C07D409/12; C07D409/12; C07D409/14; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2 | <-- |
| US 5977137 | ECLA | C07K005/06H2 | <-- |
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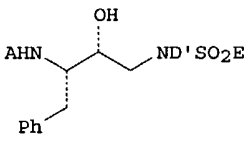
| US 2003069222 | ECLA | C07C307/06; C07D209/08; C07D213/30D; C07D215/48; C07D231/14; C07D239/22D2; C07D263/24; C07D021/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/1; C07D405/12; C07D409/12; C07D409/12; C07D409/14; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2; C07C311/13; C07C311/18; C07C311/39; C07C311/46; C07D207/26C | <-- |

OS MARPAT 126:144117

GI




I

AB The title compds. I [A = 3-tetrahydrofuryloxycarbonyl; D' = (un)substituted alkyl; E = (un)substituted aryl] are prepared This invention also relates to pharmaceutical compns. comprising these compds. The compds. and pharmaceutical compns. of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and

consequently, may be advantageously used as antiviral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting the activity of HIV aspartyl protease using the compds. of this invention and methods for screening compds. for anti-HIV activity. The title compds. inhibit HIV replication at concentration of .ltoreq. 100 nM.

ST sulfonamide prepn aspartyl protease inhibitor; HIV virucide sulfonamide prepn

IT Antiviral agents
Human immunodeficiency virus
(preparation of sulfonamide inhibitors of aspartyl protease with activity against HIV)

IT 157567-04-9P 157567-10-7P 159005-79-5P 159005-82-0P 159005-86-4P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of sulfonamide inhibitors of aspartyl protease)

IT 60-12-8, Phenethyl alcohol 74-89-5, Methylamine, reactions 75-44-5, Carbonic dichloride 78-81-9, Isobutylamine 79-22-1, Methyl chloroformate 93-10-7, Quinaldic acid 98-09-9, Benzenesulfonyl chloride 98-31-7, 3,4-Dichlorobenzenesulfonyl chloride 98-59-9, p-Toluenesulfonyl chloride 98-68-0, 4-Methoxybenzenesulfonyl chloride 98-74-8, p-Nitrobenzenesulfonyl chloride 98-79-3, L-Pyroglutamic acid 99-16-1 100-46-9, Benzylamine, reactions 100-55-0, 3-Pyridylcarbinol 105-13-5, 4-Methoxybenzyl alcohol 108-23-6, Isopropyl chloroformate 109-61-5, Propyl chloroformate 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 121-47-1, 3-Aminobenzenesulfonic acid 121-60-8, 4-Acetamidobenzenesulfonyl chloride 124-63-0, Methanesulfonyl chloride 274-09-9, 1,3-Benzodioxole 349-71-3, 3-Fluoro-4-acetamidobenzenesulfonyl chloride 453-20-3 496-16-2, 2,3-Dihydrobenzofuran 501-53-1, Benzyl chloroformate 541-41-3, Ethyl chloroformate 543-27-1, Isobutyl chloroformate 585-47-7, 1,3-Benzenedisulfonyl dichloride 586-98-1, 2-Pyridylcarbinol 612-16-8, 2-Methoxybenzyl alcohol 617-89-0, Furfurylamine 628-12-6, 2-Methoxyethyl chloroformate 638-32-4, Succinamic acid 701-99-5, Phenoxyacetyl chloride 768-09-2, 2,1,3-Benzoxadiazol-5-ol 777-44-6, 3-Trifluoromethylbenzenesulfonyl chloride 1003-03-8, Cyclopentylamine

1445-91-6, (s)-(-)-1-Phenylethanol 1483-28-9, 2,5-Dimethoxybenzenesulfonyl chloride 1517-69-7, (+)-1-Phenylethanol 1656-44-6, 2,4-Dinitrobenzenesulfonyl chloride 1885-14-9, Phenyl chloroformate 1939-99-7, .alpha.-Toluenesulfonyl chloride 2905-21-7, 2-Fluorobenzenesulfonyl chloride 2937-50-0, Allyl chloroformate 2942-58-7, Diethyl cyanophosphonate 3160-59-6 3173-56-6, Benzyl isocyanate 3218-02-8, Cyclohexanemethanamine 3445-11-2 3513-81-3, 2-Methylene-1,3-propanediol 4025-64-3, 3-Chlorosulfonylbenzoic acid 4254-02-8, Cyclopentanecarbonitrile 4319-49-7, N-Aminomorpholine 5070-13-3 5680-80-8, Serine methyl ester hydrochloride 5988-19-2, L-Dihydroorotic acid 6306-52-1, Valine methyl ester hydrochloride 6971-51-3, 3-Methoxybenzyl alcohol 7693-46-1, p-Nitrophenyl chloroformate 13360-57-1, Dimethylsulfamoyl chloride 13918-92-8, 2,4-Difluorobenzenesulfonyl chloride 15833-61-1, Tetrahydro-3-furanmethanol 16078-30-1, 1-Acetylindoline 16375-88-5, 4-Acetamidobenzyl alcohol 16420-13-6, Dimethylthiocarbamoyl chloride 16761-18-5, 4-Acetamido-3-chlorobenzenesulfonyl chloride 22037-28-1, 3-Bromofuran 23095-31-0, 3,4-Dimethoxybenzenesulfonyl chloride 24424-99-5, Di-tert-butyl pyrocarbonate 28148-54-1, 2-Methylallylamine hydrochloride 30992-29-1 30996-79-3 49584-26-1, 4-Cyanobenzenesulfonyl chloride 52467-54-6 69812-29-9, 2-Acetamido-4-methyl-5-thiazolesulfonyl chloride 80466-79-1, 3,5-Dimethylisoxazole-4-sulfonyl chloride 80466-80-4, 2,4-Dimethylthiazole-5-sulfonyl chloride 86087-23-2 86087-24-3 88986-45-2, 3-Butenyl chloroformate 94108-56-2, 4-Trifluoromethoxybenzenesulfonyl chloride 98737-29-2 126714-85-0 128018-43-9 128018-44-0 132388-57-9 151858-64-9 158627-30-6, N,N-Disuccinimidyl carbonate 160233-26-1, 4-Fluoro-3-acetamidobenzenesulfonyl chloride 160233-27-2 160233-28-3 160233-29-4 160233-30-7 169772-25-2 186463-41-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of sulfonamide inhibitors of aspartyl protease)

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of sulfonamide inhibitors of aspartyl protease)

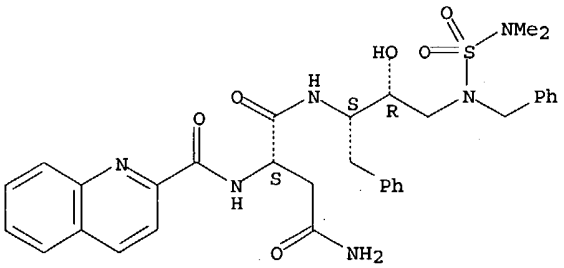
IT 78169-47-8, Aspartyl protease
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(preparation of sulfonamide inhibitors of aspartyl protease with activity against HIV)

IT **160230-15-9P 160230-25-1P 160230-31-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of sulfonamide inhibitors of aspartyl protease)

RN 160230-15-9 HCAPLUS
CN Butanediamide, N1-[(1S,2R)-3-[[(dimethylamino)sulfonyl](phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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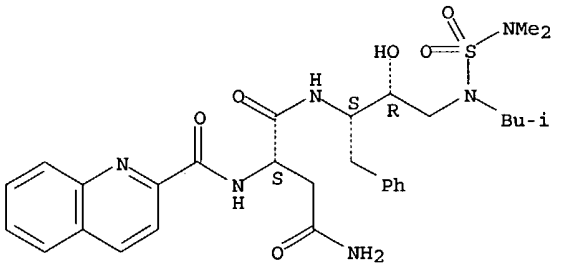
CN Butanediamide, N1-[(1S,2R)-3-[[(dimethylamino)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

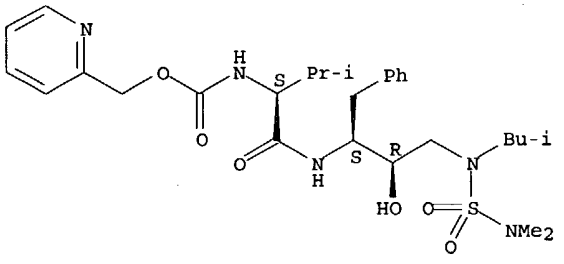


RN 160230-31-9 HCAPLUS
CN 3-Thia-2,4,8,11-tetraazadodecan-12-oic acid, 6-hydroxy-2-methyl-10-(1-methylethyl)-4-(2-methylpropyl)-9-oxo-7-(phenylmethyl)-, 2-pyridinylmethyl ester, 3,3-dioxide, (6R,7S,10S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 160230-30-8
CMF C28 H43 N5 O6 S

Absolute stereochemistry.



CM 2

CRN 76-05-1
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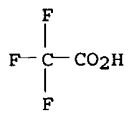

L24 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:293723 HCAPLUS
DN 122:81141
ED Entered STN: 14 Jan 1995
TI Preparation of heterocyclylarylsulfonamide inhibitors of HIV-aspartyl protease
IN Tung, Roger D.; Murcko, Mark A.; Bhisetti, Govinda Rao
PA Vertex Pharmaceuticals Inc., USA
SO PCT Int. Appl., 291 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D215-48
ICS A61K031-16; C07D413-12; C07D417-12; C07D409-14; C07D409-12; C07D213-30; C07C311-41; C07D207-26; C07D305-12; C07D239-54; C07D277-36
CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 5

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| PI WO 9405639 | A1 | 19940317 | WO 1993-US8458 | 19930907 <-- |
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| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| LT 3302 | B | 19950626 | LT 1993-917 | 19930901 <-- |
| IL 106927 | A1 | 20010111 | IL 1993-106927 | 19930906 <-- |
| EP 659181 | A1 | 19950628 | EP 1993-921428 | 19930907 <-- |
| EP 659181 | B1 | 19990407 | | |
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| JP 08501299 | T2 | 19960213 | JP 1993-507525 | 19930907 <-- |
| JP 3012002 | B2 | 20000221 | | |
| HU 71892 | A2 | 19960228 | HU 1995-685 | 19930907 <-- |
| AU 691160 | B2 | 19980514 | AU 1993-48520 | 19930907 <-- |
| AU 9348520 | A1 | 19940329 | | |
| EP 885887 | A2 | 19981223 | EP 1998-113921 | 19930907 <-- |
| EP 885887 | A3 | 19990203 | | |
| EP 885887 | B1 | 20030528 | | |
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| ES 2131589 | T3 | 19990801 | ES 1993-921428 | 19930907 <-- |
| RU 2135496 | C1 | 19990827 | RU 1995-109928 | 19930907 <-- |
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| CZ 289475 | B6 | 20020116 | CZ 1995-587 | 19930907 <-- |
| CA 2143208 | C | 20030107 | CA 1993-2143208 | 19930907 <-- |
| AT 241602 | E | 20030615 | AT 1998-113921 | 19930907 <-- |
| PL 185635 | B1 | 20030630 | PL 1993-307858 | 19930907 <-- |
| RO 118747 | B1 | 20031030 | RO 1995-479 | 19930907 <-- |
| PT 885887 | T | 20031031 | PT 1998-113921 | 19930907 <-- |
| ES 2200243 | T3 | 20040301 | ES 1998-113921 | 19930907 <-- |
| CN 1087347 | A | 19940601 | CN 1993-117370 | 19930908 <-- |
| CN 1061339 | B | 20010131 | | |
| ZA 9308470 | A | 19940620 | ZA 1993-8470 | 19931112 <-- |
| US 5585397 | A | 19961217 | US 1993-142327 | 19931124 <-- |
| FI 9501059 | A | 19950418 | FI 1995-1059 | 19950307 <-- |
| NO 9500876 | A | 19950508 | NO 1995-876 | 19950307 <-- |
| HK 1012631 | A1 | 20000623 | HK 1998-113971 | 19981217 <-- |
| PRAI US 1992-941982 | A2 | 19920908 | <-- | |

EP 1993-921428 A3 19930907
WO 1993-US8458 W 19930907

CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES |
|---|---|---|
| WO 9405639 | ICM | C07D215-48 |
| | ICS | A61K031-16; C07D413-12; C07D417-12; C07D409-14; C07D409-12; C07D213-30; C07C311-41; C07D207-26; C07D305-12; C07D239-54; C07D277-36 |
| US 5585397 | ECLA | C07D207/26C; C07D209/08; C07D213/30D; C07D215/48; C07D231/14; C07D239/22D2; C07D263/24; C07D271/08; C07D277/36; C07D307/12; C07D307/20; C07D403/12; C07D405/12; C07D405/12; C07D405/12; C07D409/12; C07D409/12; C07D409/14; C07D413/12; C07D413/12; C07D413/12; C07D413/12; C07D413/14; C07D413/14; C07D417/12; C07K005/06H2 <-- |

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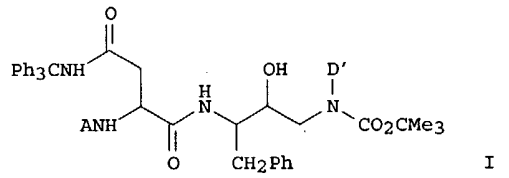


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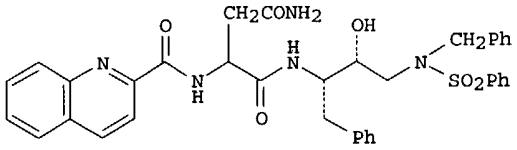


II

AB Title compds. A(B)xNHCH(D)CH(OH)CH2N(D')SO2E (A = H, Het, R1-Het, (substituted)R1-C1-6 alkyl, (substituted) R1-C2-6 alkenyl wherein R1 = CO, SO2, COCO, O2C, etc., Het = C5-7 cycloalkyl, C5-7 cycloalkenyl, C6-10 aryl, (substituted) 5-7-membered heterocyclyl; R2 = H, (Ar)-C1-3 alkyl; B = NR2CR3CO, null wherein R3 = H, (substituted)Het or C1-6 alkyl or C2-6 alkenyl or C3-6 cycloalkyl or C5-6 cycloalkenyl; x = 0,1; D, D' = Ar, (substituted) C1-4 alkyl wherein Ar = Ph, (substituted) 3-6-membered carbocyclyl or 5-6-membered heterocyclyl; E = Het-O, Het-Het, (substituted) C1-6 alkyl or C2-6 alkenyl, C3-6 carbocyclyl) useful also against viral infection of HIV-2, HIV-2, or HTLV, are prepared 4,3-(AcNH)FC6H3SO2Cl and syn-I (A = quinolin-2-ylcarbonyl, D' = Me2CHCH2) (preparation given) in CH2Cl2 was treated with F3CCO2H followed by NaHCO3 and 4-FC6H4SO2Cl to give the title compound II which inhibited HIV-1 protease with IC50 of <0.1 nM.

ST heterocyclylarylsulfonamide prepn antiviral; aspartyl protease HIV inhibition heterocyclylarylsumfonamide; HIV treatment heterocyclylarylsumfonamide

IT Virucides and Virustats
(sulfonamide inhibitors of HIV-aspartyl protease)

IT Sulfonamides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(sulfonamide inhibitors of HIV-aspartyl protease)

IT Virus, animal
(human T-cell leukemia, inhibitors, heterocyclylarylsulfonamides)

IT Virus, animal
(human immunodeficiency 1, inhibitors, heterocyclylarylsulfonamides)

IT Virus, animal
(human immunodeficiency 2, inhibitors, heterocyclylarylsulfonamides)

IT 78169-47-8, Aspartic proteinase
RL: RCT (Reactant); RACT (Reactant or reagent)
(of HIV-1, inhibitors, heterocyclylarylsulfonamides)

IT 1080-11-1P 1828-66-6P, 4-Morpholinesulfonyl chloride 4295-99-2P 6053-81-2P, Cyclopentanemethanamine 23905-46-6P 25506-37-0P

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(Reactant or reagent)
(preparation and reaction of, in preparation of HIV-1 protease inhibitors)

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160333-45-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of as HIV-1 protease inhibitor)

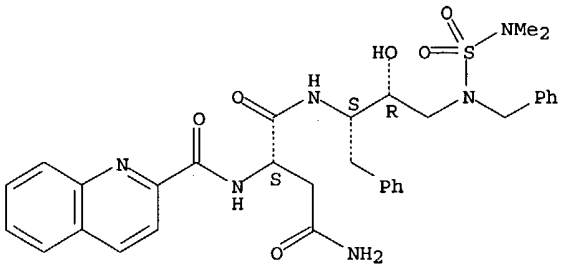
IT 60-12-8, Phenethyl alcohol 78-81-9, Isobutylamine 93-10-7, Quinaldic acid 98-31-7, 3,4-Dichlorobenzenesulfonyl chloride 98-68-0, 4-Methoxybenzenesulfonyl chloride 98-79-3 99-16-1 100-55-0, 3-Pyridyl carbinol 105-13-5, 4-Methoxybenzyl alcohol 108-23-6, Isopropyl chloroformate 109-61-5, n-Propyl chloroformate 110-89-4, Piperidine, reactions 121-47-1, 3-Aminobenzenesulfonic acid 121-60-8, N-Acetylsulfanilyl chloride 274-09-9, 1,3-Benzodioxole 349-71-3, 3-Fluoro-4-acetamidobenzenesulfonyl chloride 349-88-2, 4-Fluorobenzenesulfonyl chloride 453-20-3, (RS)-3-hydroxytetrahydrofuran 496-16-2, 2,3-Dihydrobenzofuran 501-53-1, Benzyl chloroformate 513-42-8, Methallyl alcohol 543-27-1, Isobutyl chloroformate 585-47-7, 1,3-Benzenedisulfonyl dichloride 586-95-8, 4-Pyridyl carbinol 586-98-1, 2-Pyridyl carbinol 612-16-8, 2-Methoxybenzyl alcohol 617-89-0, Furfurylamine 628-12-6, 2-Methoxyethyl chloroformate 638-32-4, Succinamic acid 701-99-5, Phenoxyacetyl chloride 768-09-2, Benzofurazan-5-ol 777-44-6, 3-(Trifluoromethyl)benzenesulfonyl chloride 946-80-5, Benzyl phenyl ether 1003-03-8, Cyclopentylamine 1445-91-6 1483-28-9, 2,5-Dimethoxybenzenesulfonyl chloride 1493-13-6, Trifluoromethanesulfonic acid 1517-69-7 1656-44-6, 2,4-Dinitrobenzenesulfonyl chloride 1885-14-9, Phenyl chloroformate 2799-21-5 2905-21-7, 2-Fluorobenzenesulfonyl chloride 2937-50-0, Allyl chloroformate 3160-59-6 3173-56-6, Benzyl isocyanate 3445-11-2, 1-(2-Hydroxyethyl)-2-pyrrolidinone 3513-81-3, 2-Methylene-1,3-propanediol 4025-64-3, 3-(Chlorosulfonyl)benzoic acid 4254-02-8, Cyclopentanecarbonitrile 4319-49-7, N-Aminomorpholine 5070-13-3 5680-80-8, Serine methyl ester hydrochloride 5988-19-2, L-Dihydroorotic acid 6306-52-1, Valine methyl ester hydrochloride 6971-51-3, 3-Methoxybenzyl alcohol 7252-53-1, Cyclopropylmethylamine hydrochloride 7633-32-1 7693-46-1, p-Nitrophenyl chloroformate 13258-63-4, 4-Pyridineethanamine 13360-57-1, Dimethylsulfamoyl chloride 13918-92-8, 2,4-Difluorobenzenesulfonyl chloride 16078-30-1, 1-Acetylindoline 16375-88-5, 4-Acetamidobenzyl alcohol 16420-13-6, Dimethylthiocarbamoyl chloride 16761-18-5, 4-Acetamido-3-chlorobenzenesulfonyl chloride 22037-28-1, 3-Bromofuran 23095-31-0, 3,4-Dimethoxybenzenesulfonyl chloride 24424-99-5, Di-tert-butyl pyrocarbonate 28148-54-1 30992-29-1 52467-54-6 69812-29-9, 2-Acetamido-4-methyl-5-thiazolesulfonyl chloride 74124-79-1, N,N'-Disuccinimidyl carbonate 80466-79-1, 3,5-Dimethylisoxazole-4-sulfonyl chloride 80466-80-4, 2,4-Dimethylthiazole-5-sulfonyl chloride 86087-23-2, (S)-(+)-3-Hydroxytetrahydrofuran 88986-45-2 94108-56-2 98737-29-2 126714-85-0 128018-43-9 128018-44-0 132388-57-9 145758-05-0, 3,4-Difluorobenzenesulfonyl chloride 151858-64-9 160232-67-7 160233-25-0 160233-26-1, 4-Fluoro-3-acetamidobenzenesulfonyl chloride 160233-27-2 160233-28-3 160233-29-4 160233-30-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of HIV-1 protease inhibitors)

IT **160230-15-9P 160230-25-1P 160230-31-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of as HIV-1 protease inhibitor)

RN 160230-15-9 HCAPLUS

CN Butanediamide, N1-[(1S,2R)-3-[[(dimethylamino)sulfonyl](phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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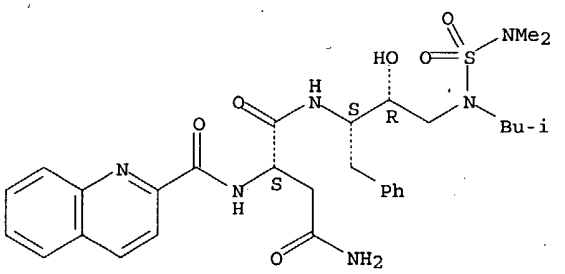
CN Butanediamide, N1-[(1S,2R)-3-[[(dimethylamino)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

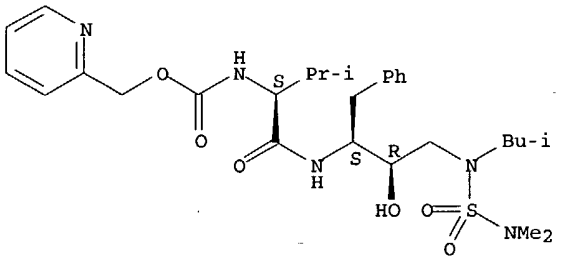


RN 160230-31-9 HCAPLUS
CN 3-Thia-2,4,8,11-tetraazadodecan-12-oic acid, 6-hydroxy-2-methyl-10-(1-methylethyl)-4-(2-methylpropyl)-9-oxo-7-(phenylmethyl)-, 2-pyridinylmethyl ester, 3,3-dioxide, (6R,7S,10S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

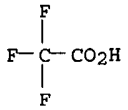
CRN 160230-30-8
CMF C28 H43 N5 O6 S

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



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FILE LAST UPDATED: 14 Oct 2004  (20041014/ED)

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AN   1996:725344  HCAPLUS
DN   126:75247
ED   Entered STN:  11 Dec 1996
TI   Preparation of .alpha.- and .beta.-amino acid hydroxyethylamino sulfonyl
     urea derivatives as retroviral protease inhibitors
IN   Vazquez, Michael L.; Mueller, Richard A.; Talley, John J.; Getman, Daniel
     P.; Decrescenzo, Gary A.; Sun, Eric T.
PA   G.D. Searle and Co., USA
SO   U.S., 37 pp.
     CODEN: USXXAM
DT   Patent
LA   English
IC   ICM  C07D401-12
     ICS  C07D413-12; C07D417-12; A61K031-47; A61K031-505; A61K031-54
NCL  514314000
CC   34-3 (Amino Acids, Peptides, and Proteins)
     Section cross-reference(s): 1, 7, 63
FAN.CNT 1
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     US 6022872           A     20000208    US 1996-709069           19960906
     US 6211176           B1    20010403    US 1999-345739           19990701
     US 6403585           B1    20020611    US 2000-731911           20001208
     US 2003144342        A1    20030731    US 2002-138534           20020506
     US 6683648           B2    20040127
     US 2004174653        A1    20040902    US 2003-689513           20031021
PRAI US 1992-968712       A3    19921030
     US 1996-709069       A1    19960906
     US 1999-345739       A1    19990701
     US 2000-731911       A1    20001208
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US 2002-138534 A1 20020506

CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES |
|---|---|---|
| US 5578606 | ICM | C07D401-12 |
| | ICS | C07D413-12; C07D417-12; A61K031-47; A61K031-505; A61K031-54 |
| | NCL | 514314000 |
| US 5578606 | ECLA | C07C307/06; C07D239/38; C07D307/85; C07K005/06A1A1; C07K005/06A1A3; C07K005/06H2; C07K005/06T; C07D023/42C; C07D215/48; C07D215/50; C07D215/54; C07D235/06B |
| US 6403585 | ECLA | C07C307/06; C07D213/42C; C07D215/48; C07D215/50; C07D215/54; C07D235/06B; C07D239/38; C07D030/85; C07K005/06A1A3; C07K005/06A1A1; C07K005/06H2; C07K005/06T |
| US 2003144342 | ECLA | C07C307/06; C07D213/42C; C07D215/48; C07D215/50; C07D215/54; C07D235/06B; C07D239/38; C07D030/85; C07K005/06A1A3; C07K005/06A1A1; C07K005/06H2; C07K005/06T |

OS MARPAT 126:75247

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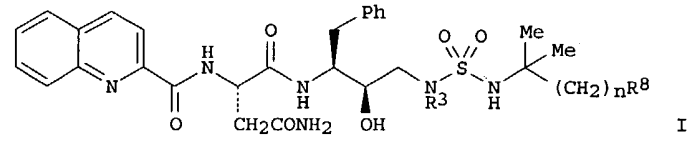

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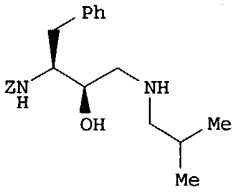

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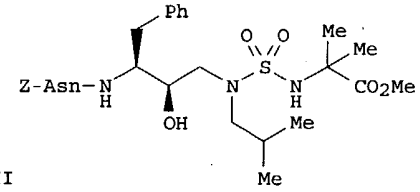

III

AB .alpha.- And .beta.-amino acid hydroxyethylamino sulfonyl urea derivative compds., e.g. I [R3 = C1-8 alkyl, (un)substituted C1-8 alkylphenyl, C1-8 heteroaralkyl; R8 = (un)substituted Ph, heterocyclyl, CN, OH, CO2H, C1-8 alkylthio, (un)substituted phenylsulfonyl, C1-8 alkanoyl, C1-8 alkoxycarbonyl, C1-8 dialkylaminocarbonyl, N-C1-8- alkyl-N-phenylcarbamoyl, 2-heterocyclylethoxy, heterocyclyl; n = 0-2], are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease. Thus, coupling of protected amino(hydroxy)phenylbutylamine II (Z = PhCH2O2C) (prepared in 3 steps from chloromethyl ketone Z-L-Phe-CH2Cl) with ClSO2NHCMe2CO2Me, followed by hydrogenolysis and coupling with Z-Asn-OH gave inhibitor III.

ST retroviral protease inhibitor hydroxyethylaminosulfonyl urea peptide; protease inhibitor hydroxyethylaminosulfonyl urea peptide prepn; HIV virucide hydroxyethylaminosulfonyl urea peptide prepn

IT Antiviral agents
Human immunodeficiency virus 1
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT 185256-67-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT 63-91-2, L-Phenylalanine, reactions 78-81-9, Isobutylamine 105-13-5, 4-Methoxybenzyl alcohol 107-85-7, Isoamylamine 2170-03-8 2304-96-3 26049-94-5 152714-71-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT 107-95-9P, .beta.-Alanine 498-25-9P 541-48-0P, 3-Aminobutanoic acid 3377-31-9P 3653-34-7P 4385-92-6P 5699-54-7P 15099-85-1P 16934-21-7P 32723-74-3P 32723-76-5P 53874-24-1P 60427-77-2P

65414-77-9P 75081-40-2P 83509-04-0P 91247-38-0P 95598-13-3P
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132696-45-8P 143224-62-8P 143224-86-6P 143225-04-1P 160191-57-1P
185256-61-5P 185256-62-6P 185256-63-7P 185256-64-8P 185256-65-9P
185256-66-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

IT 9001-92-7, Protease
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(retroviral; preparation of hydroxyethylamino sulfonyl urea peptide derivs. as retroviral protease inhibitors)

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MOST RECENT DERWENT UPDATE: 200465 <200465/DW>
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L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2004-651696 [63] WPIX
CR 1997-020446 [02]; 2000-160388 [14]; 2001-388432 [41]; 2002-573171 [61]; 2004-118988 [12]
DNC C2004-233217
TI New alpha- and beta-amino acid hydroxyethylamino sulfonyl urea derivatives useful as retroviral protease inhibitors in the treatment of AIDS.
DC B05
IN DECRESCENZO, G A; GETMAN, D P; MUELLER, R A; SUN, E T; TALLEY, J J; VAZQUEZ, M L
PA (SEAR) SEARLE & CO G D
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PI US 2004171653 A1 20040902 (200463)* 44 A61K031-44 <--
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US 2002-138534 20020506; US 2003-689513 20031021
IC ICM A61K031-44
ICS A61K031-40; C07C381-06
AB US2004171653 A UPAB: 20041001
NOVELTY - Alpha- and beta-amino acid hydroxyethylamino sulfonyl urea derivatives (I) are new.
DETAILED DESCRIPTION - Alpha- and beta-amino acid hydroxyethylamino sulfonyl urea derivatives of formula (I) are new.
R = H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxyalkyl, aralkyloxycarbonyl,

(cyclo)alkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and di-substituted aminocarbonyl and mono- and di-substituted aminoalkanoyl radicals (the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or when the aminoalkanoyl radical is disubstituted, the substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical);

R' = H, R3 or R3SO2;

N(R)R' = heterocycloalkyl or heteroaryl radicals;

R1 = -CH2SO2NH2, -CH2CO2CH3, -CO2CH3, -CONH2, -CH2C(O)NHCH3, -C(CH3)2(SH), -C(CH3)2(SCH3), -C(CH3)2(S(O)CH3), -C(CH3)2(S(O)2CH3), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cysteine and methionine and its sulfoxide (SO) and sulfone (SO2) derivatives, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-methyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

R1' and R1'' = H or R1;

CR1'+CR1 or CR1+CR1'' = cycloalkyl radical;

R2 = alkyl, aryl, cycloalkyl, cycloalkylalkyl or aralkyl (optionally substituted by alkyl and halo radicals, -NO2, -CN, -CF3, -OR9 or -SR9);

R9 = H, alkyl or halo;

R3 = alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl, and mono- and disubstituted aminoalkyl radicals (the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals or in the case of a disubstituted aminoalkyl radical, the substituents along with the nitrogen atom to which they are attached form heterocycloalkyl or heteroaryl), and thioalkyl, alkylthioalkyl and arylthioalkyl and their sulfone and sulfoxide derivatives;

R4, = H or R3;

R6 = H or alkyl;

R7 and R7' = H, R3, amino acid side chains selected from valine, isoleucine, glycine, alanine, allo-isoleucine, asparagines, leucine, glutamine or tert-butylglycine, -C(O)R16, -CO2R16, -SO2R16, -SR16, -CONR16R17, -CF3 or -NR16R17;

CR7R7' = cycloalkyl;

R8 = cyano, hydroxyl, alkyl, alkoxy, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, C(O)R16, CO2R16, SO2R16, SR16, CONR16R17, CF3 or NR16R17;

R15, R16 and R17 = H or R3;

NR16R17 = heterocycloalkyl or heteroaryl;

x = 1 or 2;

n = 0 - 6;

t = 0 - 2; and

Y = O, S or NR15.

An INDEPENDENT CLAIM is included for a sulfonyl urea derivative of formula (II).

P1 = H, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals, (the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or when aminoalkanoyl radical is disubstituted, the substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical);

P2 = H or R3;

NP1P2 = heterocycloalkyl or heteroaryl;

R8' = cyano, hydroxyl, alkyl, alkoxy, cycloalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl radicals and radicals represented by C(O)R16, CO2R16, SO2R16, SR16, CONR16R17, -CF3 and NR16R17.

ACTIVITY - Virucide.

MECHANISM OF ACTION - HIV Protease inhibitor; Retroviral protease inhibitor.

USE - For treating retroviral infection e.g. HIV infection and AIDS (claimed).

ADVANTAGE - The compounds are potent retroviral protease inhibitors.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B10-A08; B14-A02B1; B14-D07C; B14-G01B